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Recipes Research

Research ideas and strategies on the dose-effect relationship of traditional Chinese medicine prescriptions and herbs

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Abstract

We discuss here the complexity of the doses of traditional Chinese medicine (TCM) prescriptions and herbs from different viewpoints, including the heterogeneity of drug quality, the flexibility of prescriptions, and the diversity of drug effects. Then, the corresponding research ideas and strategies are proposed. We can reveal the actual situation of clinical doses based on in-depth "real-world study" of the safety and effectiveness of TCM prescriptions, create an analytical method for dose-effect relationships in accordance with the features of TCM, and reveal the correlated regular nature of the effectiveness and dosage of TCM prescriptions and herbs.

Key words: Traditional chinese medical prescriptions and herbs; Dose-effect relationship; Modeling methods of complex systems

INTRODUCTION

Traditional Chinese medicine (TCM) differs to cut crude drug and Chinese patent medicine with respect to form of usage. The cut crude drug is the major form of application of TCM, and its dosage is the key problem in the research on TCM dosages. Therefore, the present study focuses on explaining the dose-effect relationship of cut crude drugs. The dose-effect relationship of TCM is different from that of pharmaceutical chemicals in certain characteristics. Based on the features of TCM, one of the key problems is understanding the "secret of the dose of TCM" in order to introduce new methods.

Complexity of the dose of TCM prescriptions and herbs

TCM arises from natural products. Most are vegetable-based drugs which grow in different environments. Hence, the qualities of the drugs are not uniform. In the clinic, studying the dosages of TCM prescriptions and herbs is difficult because of the: 1) different pathogenetic conditions and syndromes; 2) features of individual diagnoses and use of TCM; 3) diversity of drug effects; 4) flexibility of TCM prescriptions; 5) influence of drug processing; 6) approaches of decoction or caplendus.

Non-uniformity of the qualities of Chinese crude drugs: Studies have indicated that vegetable-based drugs have different chemical compositions due to differences in biocoenosis[1,2]. Some researchers evaluated reports about the chemical compositions of TCMs (e. g., Gan Cao (Radix et Rhizoma Glycyrrhizae), Da

Huang (Radix et Rhizoma Rhei), Shao Yao (Chinese herbaceous peony), Huang Qin (Radix Scutellariae), Huang Qi (Radix Astragali), Cang Zhu (Rhizoma Atractylodis)) to reveal that the compositions had considerable differences[3]. Owing to the different compositions of drugs, drug actions show diversity[4-6].

Flexibility of TCM prescriptions: In practice, TCM physicians select the most suitable drugs according to the disease, syndrome, and symptoms. TCM prescriptions vary according to the condition, and the drug dosage is an important part of the prescription. The same drug has different doses due to different positions. For example, *Materia Medica of Decoction* states that the "principal drug" is the most, "ministerial drug" is the second most important, and "adjunctive drug" is the next in order.

Different medical schools have differing views on the dose of TCM prescriptions. Until now, there have been distinctions in the doses of certain drugs (e.g., Wu Tou (Radix Aconiti), Fu Zi (Radix Aconiti Lateralis Praeparata), Da Huang (Radix et Rhizoma Rhei), Shi Gao (Gypsum Fibrosum), Ma Huang (Herba Ephedrae), Di Huang (Radix Rehmanniae), and Ban Xia (Rhizoma Pinelliae)). There are a few ingredients in a prescription, but the dose of each ingredient can be appreciable, and *vice versa*[7].

Diversity of drug and prescription effects: The effects of TCM not only have one target or symptom, but also miscellaneous targets or symptoms. Many TCM agents have several effects. For example, Ma Huang induces sweat and dispels exogenous evils, facilitates the flow of gastric *Qi* to relieve asthma, and induces diuresis to alleviate edema. Drug dosage is associated with drug effects. For example, Chai Hu can promote *Qi* at lower dosages, dispel gloom in medium dosages, and lower pyretolysis at high dosages. There are many similar cases[8,9]. The effects of TCM prescriptions are more complex. The diversity of drug and prescription effects has advanced the flexibility of TCM prescriptions, but simultaneously aggravated the complexity of research into dose-effect relationships. The different effects of drugs resulting from different dosages, and the diversity of drug and prescription effects have influenced evaluation of the dose-effect relationships of drugs.

Influence of drug processing and the approaches of decoction or caplendus: The dosage of TCM prescriptions and herbs is relevant to the processing of drugs and the approaches of decoction or caplendus. Appropriate processing of drugs can improve their effects and reduce toxicity. Some drugs have different actions after processing, so the dosage of drug will also change. For example, Dai Huang can be used to open the bowels at low doses, and promote blood flow at high doses. In addition, the time and intensity of decoction can lead to changes in the active ingredients of the prescription. Studies have indicated that the content of tanshinol and protocatechualdehyde in Dan Shen root is low but, with increasing decoction time, the content of salvianolic acid B is reduced, and the content of tanshinol and protocatechualdehyde is increased[10]. The content of saffron acid I in the Cape jasmine fruit of Coptidis decoction for detoxification increased after decocting together, and decreased with increasing decoction time[11]. The approaches of caplendus also influence drug dose. As stated in *A Treatise on Febrile Diseases*, "if the disease has not been cured after decoction, it continues to caplendus". That is, physicians determine the dose of drugs to add or reduce based on the reaction of the patients after taking the medicine.

Research ideas and strategies on the dose-effect relationships of TCM prescriptions and herbs

We must identify the dose of TCM prescriptions and herbs if we undertake the research into the dose-effect relationships of prescriptions and herbs. Therefore, we should: reveal the "real" situation of clinical doses based on "real-world study"; research in-depth the safety and effectiveness of TCM prescriptions; create an analytical method of dose-effect relationships in accordance with the features of TCM; reveal the correlation between the effectiveness and dosages of TCM prescriptions and herbs.

Research of clinical dose based on real-world study: Real-world study is a development of pharmacoepidemiology. This method can avoid interference in the medication, is aimed directly at the particular use of the medication, and the results can have practical uses[12,13]. The doses of TCM prescriptions and herbs arise from clinical practice. They should reveal the actual situation and regularity of the clinical dose through rational design and statistical analyses. We studied the actual dosages of clinical prescriptions in TCM, and made use of stratified sampling and random sampling methods to investigate >430,000 broth prescriptions in 21 hospitals and 18 provinces. We constructed a database, and then applied Weka KDD data-mining software (Weka; Waikato, Hamilton, New Zealand) to analyze the results. We identified the frequency and clinical = dosage intervals of 300 drugs, and the practical dosage of 152 drugs whose dose was different in actuality and in the Chinese Pharmacopoeia (2005 edition)[14-19].

Research into dose-effect relationships of TCM prescriptions and herbs based on laboratory analyses

It is important to study the safety and availability of drugs after clinical investigations. We must construct methods to analyze the dose-effect relationships of

TCM to reveal the regular nature of the effects and the doses of TCM prescriptions and herbs.

Development of methods to analyze the dose-effect relationships of TCM: Introducing new methods to analyze the dose-effect relationships of TCM is important. The focus is to establish reciprocal evaluation methods of drug action. The entropy theory and two-model fuzzy theory are methods used to study the connection between various types of characteristic variables. These can reveal the non-linear relationship between the dose and the effect of TCM prescriptions and herbs.

Complex prescriptions are the principal medicinal style, and have different effects (e.g., one target, or more than one target). The key problem is to explore the methods to analyze dose-effect relationships as one target, more drugs; or more targets, more drugs. Mathematical statistical methods such as Lasso multiple regression[20], neural networks based on entropy[21], optimized methods on account of Ant Group Algorithms, and two-model fuzzy logic[22,23], could solve the problem, and be used to construct mathematic models between the dose and one target of drug action. With regard to more targets, we could take linear and non-linear methods (just as in the method of principal component analysis) and generalize targets to extract the synthetic characteristics respectively. We could then transform more targets to one target, and analyze the dose-effect relationships of TCM prescriptions and herbs.

Revealing the reproducibility of the connection between the dose and effect of TCM prescriptions and herbs: Rivalry and adjustment are the elementary modes of drug action. The effect of rivalry displays the mode "exclusive effect and spacious action". The effect of adjustment displays the mode "extensive effects and ingenious action". We could initially apply different methods to construct the mathematic model associated with more drugs and one target. We could then use the methods to mix together or relate mathematic models. We should ignore, as much as possible, the other targets and focus on the outstanding single important target of drug action which displays the mode "exclusive effect and spacious action". Simultaneously, we could use methods to extract the synthetic characteristics, and transform more targets to one target, then pursue a good level to targets of drug action which displays the mode "extensive effects and ingenious action". We could apply the methods of Lasso multiple regression, neural networks based on entropy, optimize methods on account of Ant Group Algorithms and two-model fuzzy logic to ascertain the best matching of drugs and dosage. We can reveal the regular nature of the effect and dose of TCM prescriptions and herbs through such mathematical methods to provide the basis of the clinical use of TCM.

To translate empirical research into clinical practice based on study of dose-effect relationships

Evaluation of dose-effect relationships in practice is the best way to optimal drug dosage. Results of studies of drug dosages based on real-world study can be used to identify the clinical-dosage intervals of frequently used drugs, which will provide the basis for the dose of clinical prescriptions. Furthermore, we can analyze the results and summarize the regular nature of effect and dosage.

Summary

Research into the dose-effect relationships of TCM is very important. Based on the results of real-world study mathematical modeling, as well as reference to the Chinese *Materia medica*, pharmacology, chemistry, epidemiology, and statistics, optimal drug dosages for TCM prescriptions and herbs can be realized.

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